(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 January 2005 (06.01.2005)

PCT

(10) International Publication Number
WO 2005/000846 A1

(51) International Patent Classification[7]: C07D 471/04, A61K 31/4745, A61P 5/50

(21) International Application Number: PCT/EP2004/006336

(22) International Filing Date: 11 June 2004 (11.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03013405.0 20 June 2003 (20.06.2003) EP

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

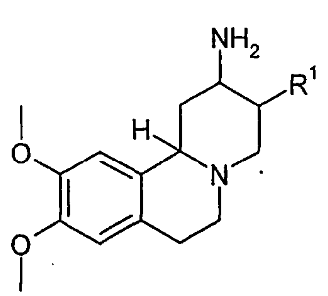
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/000846 A1

(54) Title: HEXAHYDROPYRIDOISOQINOLINES AS DPP-IV INHIBITORS



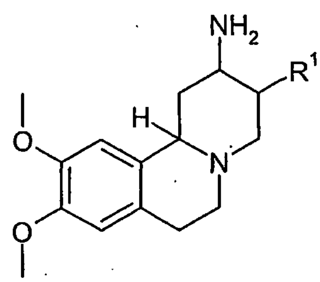
(I)

(57) Abstract: The present invention relates to compounds of formula (I) wherein R^1 is as defined in the description and claims, and pharmaceutically acceptable salts thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with DPP-IV, such as diabetes, particularly non-insulin dependent diabetes mellitus, and impaired glucose tolerance.

HEXAHYDROPYRIDOISOQINOLINES AS DPP-IV INHIBITORS

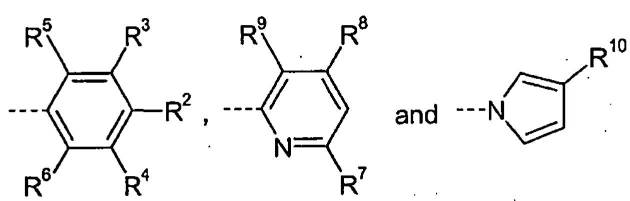
The present invention is concerned with novel pyrido[2,1-a]isoquinoline derivatives, their manufacture and their use as medicaments.

In particular, the invention relates to compounds of the formula (I)



wherein

R^1 is selected from



R^2 is hydrogen or lower alkoxy;

R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, lower alkyl, halogenated lower alkyl, halogen or cycloalkyl; provided that R^2, R^3, R^4, R^5 and R^6 are not all hydrogen;

R^7, R^8 and R^9 are each independently hydrogen, lower alkyl, lower alkoxy, lower hydroxyalkyl or halogenated lower alkyl; provided that R^7, R^8 and R^9 are not all hydrogen;

R^{10} is lower alkyl or halogenated lower alkyl;

and pharmaceutically acceptable salts thereof.

The enzyme dipeptidyl peptidase IV (EC.3.4.14.5, abbreviated in the following as DPP-IV) is involved in the regulation of the activities of several hormones. In particular DPP-IV is degrading efficiently and rapidly glucagon like peptide 1 (GLP-1), which is one of the most potent stimulator of insulin production and secretion. Inhibiting DPP-IV would potentiate the effect of endogenous GLP-1, and lead to higher plasma insulin concentrations. In patients suffering from impaired glucose tolerance and type 2 diabetes mellitus, higher plasma insulin concentration would moderate the dangerous hyperglycaemia and accordingly reduce the risk of tissue damage. Consequently, DPP-IV inhibitors have been suggested as drug candidates for the treatment of impaired glucose tolerance and type 2 diabetes mellitus (e.g. Villhauer, WO98/19998). Other related state of the art can be found in WO 99/38501, DE 19616486, DE 19834591, WO 01/40180, WO 01/55105, US 6110949, WO 00/34241 and US6011155.

We have found novel DPP-IV inhibitors that very efficiently lower plasma glucose levels. Consequently, the compounds of the present invention are useful for the treatment and/or prophylaxis of diabetes, particularly non-insulin dependent diabetes mellitus, and/or impaired glucose tolerance, as well as other conditions wherein the amplification of action of a peptide normally inactivated by DPP-IV gives a therapeutic benefit. Surprisingly, the compounds of the present invention can also be used in the treatment and/or prophylaxis of obesity, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, and/or metabolic syndrome or β-cell protection. Furthermore, the compounds of the present invention can be used as diuretic agents and for the treatment and/or prophylaxis of hypertension. Unexpectedly, the compounds of the present invention exhibit improved therapeutic and pharmacological properties compared to other DPP-IV inhibitors known in the art, such as e.g. in context with pharmacokinetics and bioavailability.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to six, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine and chlorine being preferred. Most preferred halogen is chlorine.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon

atoms. The term "lower alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to six carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like. Preferable lower alkyl residues are methyl and ethyl, with methyl being especially preferred.

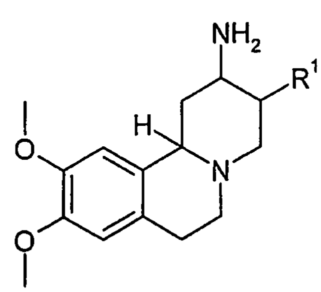
The term “halogenated lower alkyl” refers to a lower alkyl group wherein at least one of the hydrogens of the lower alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Among the preferred halogenated lower alkyl groups are trifluoromethyl, difluoromethyl, fluoromethyl and chloromethyl, with fluoromethyl being especially preferred.

The term "alkoxy" refers to the group R'-O-, wherein R' is alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is lower alkyl. Examples of lower alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy, with methoxy being especially preferred.

The term "cycloalkyl" refers to a monovalent carbocyclic radical of three to six, preferably three to five carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, with cyclopropyl being preferred.

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

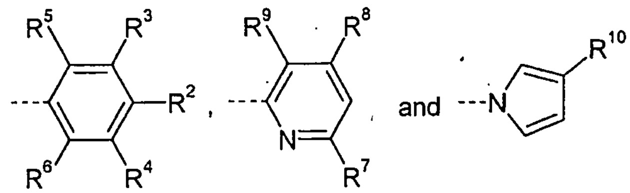
In one embodiment, the present invention relates to compounds having the formula (I)



(I)

wherein

R^1 is selected from



R^2 is hydrogen or lower alkoxy;

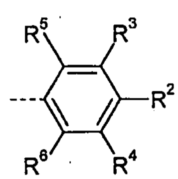
R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, lower alkyl, halogenated lower alkyl, halogen or cycloalkyl; provided that R^2, R^3, R^4, R^5 and R^6 are not all hydrogen;

R^7, R^8 and R^9 are each independently hydrogen, lower alkyl or lower alkoxy; provided that R^7, R^8 and R^9 are not all hydrogen;

R^{10} is lower alkyl or halogenated lower alkyl;

and pharmaceutically acceptable salts thereof.

In one embodiment, R^1 is



wherein R^2 is hydrogen or lower alkoxy and R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, lower alkyl, halogenated lower alkyl, halogen or cycloalkyl; provided that R^2, R^3, R^4, R^5 and R^6 are not all hydrogen.

Preferable lower alkoxy residue R^2 is methoxy.

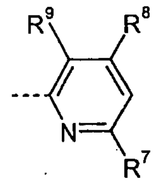
Preferable lower alkyl residues in R^3, R^4, R^5 and R^6 are methyl, ethyl, and isopropyl, with methyl being especially preferred. Preferable halogenated lower alkyl residue in R^3, R^4, R^5 and R^6 is fluoromethyl. Preferable halogen residue in R^3, R^4, R^5 and R^6 is chloro. Preferable cycloalkyl residue in R^3, R^4, R^5 and R^6 is cyclopropyl.

In one preferable embodiment, R^2, R^4, R^5 and R^6 are hydrogen and R^3 is lower alkyl, halogenated lower alkyl, halogen or cycloalkyl, with lower alkyl such as methyl or

ethyl, halogenated lower alkyl such as fluoromethyl or halogen such as chloro being especially preferred.

In another preferable embodiment, R^2, R^4 and R^5 are hydrogen and R^3 and R^6 are each independently lower alkyl, halogenated lower alkyl, halogen or cycloalkyl, with lower alkyl such as methyl or halogen such as chloro being especially preferred.

In another embodiment of the present invention, R^1 is



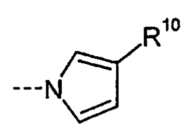
wherein R^7, R^8 and R^9 are each independently hydrogen, lower alkyl, lower alkoxy, lower hydroxyalkyl or halogenated lower alkyl; provided that R^7, R^8 and R^9 are not all hydrogen.

Preferable lower alkyl residues in R^7, R^8 and R^9 are methyl and ethyl, with methyl being especially preferred. Preferable lower alkoxy residue in R^7, R^8 and R^9 is methoxy.

In a preferable embodiment, R^7 and R^9 are hydrogen and R^8 is lower alkyl such as methyl or ethyl, or lower alkoxy such as methoxy.

In a further preferable embodiment, R^7 and R^9 are hydrogen and R^8 is lower hydroxyalkyl such as hydroxymethyl, or halogenated lower alkyl such as fluoromethyl.

In still another embodiment of the present invention, R^1 is



wherein R^{10} is lower alkyl or halogenated lower alkyl.

Preferable lower alkyl residues R^{10} are methyl and ethyl, with methyl being especially preferred. Preferable halogenated lower alkyl residue R^{10} is fluoromethyl.

Preferred compounds of general formula (I) are those selected from the group consisting of:

rac-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ylamine hydrochloride,

rac-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

9,10-dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

9,10-dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

9,10-dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-(6-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(6-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-9,10-dimethoxy-3β-(5-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(5-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-9,10-dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

9,10-dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(4-ethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-ethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(3-cyclopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(6-methoxy-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-isopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(3-cyclopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-methoxy-2-methyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyrrol-1-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine hydrochloride,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride,

rac-[2-(2α-amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-3β-yl)-pyridin-4-yl]-methanol,

rac-3β-(4-fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride,

rac-3β-(4-fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

and pharmaceutically acceptable salts thereof.

Especially preferred compounds of general formula (I) are those selected from the group consisting of:

9,10-dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine hydrochloride,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride,

rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

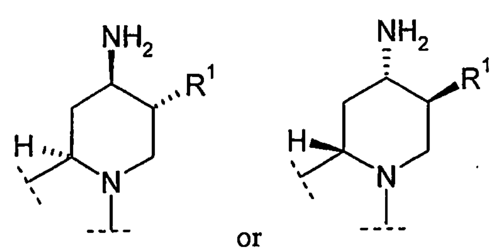
rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyrrol-1-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

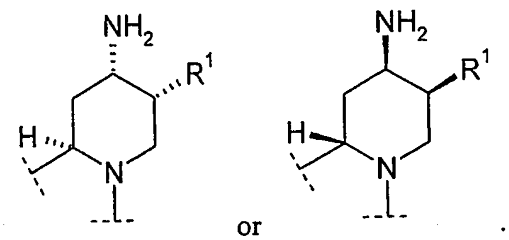
and pharmaceutically acceptable salts thereof.

The compounds of formula I have three or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of diastereomers, racemates, or mixtures of diasteroisomeric racemates. The invention embraces all of these forms.

In a preferable embodiment, R^1 and the hydrogen in position 11b of the pyrido[2,1a]isoquinoline backbone are in cis-configuration, whereas the amino group in position 2 of the pyrido[2,1a]isoquinoline backbone is in trans- configuration, i.e.



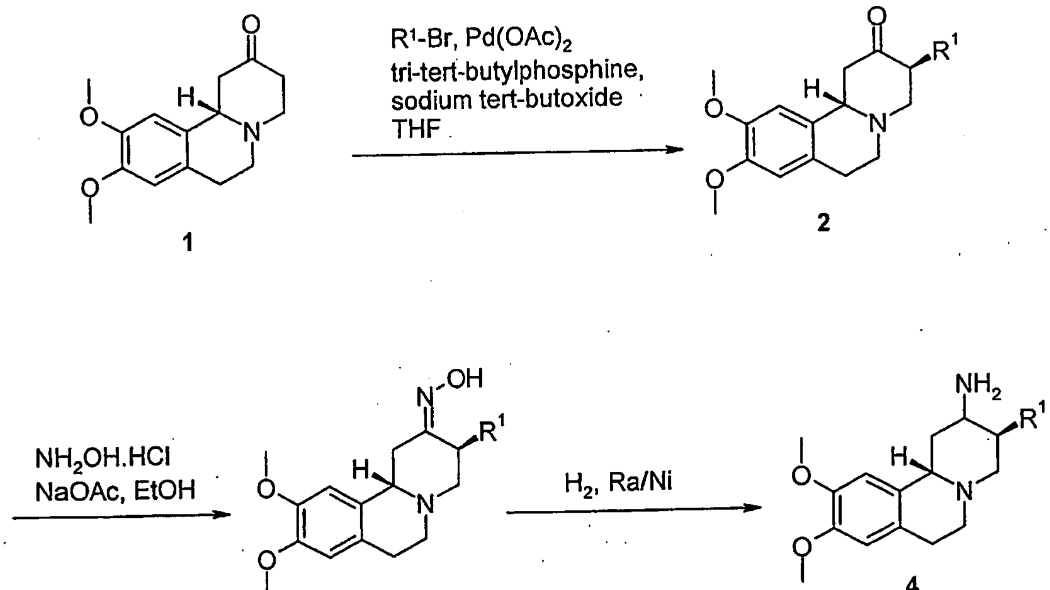
In another preferable embodiment, R^1, the amino group in position 2 and the hydrogen in position 11b of the pyrido[2,1a]isoquinoline backbone are all in cis-configuration, i.e.



It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

The present invention also relates to a process for the manufacture of compounds of formula I. The compounds of the present invention can be prepared as indicated in Schemes 1 and 2 below:

Scheme 1



The synthesis of 3-phenyl and 3-pyridyl derivatives 4 is outlined in Scheme 1 and can be achieved using the ketone 1 as starting material, a compound well known in the art [Chem. Ber. 95, 2132 (1962)]. Reaction of 1 with an aryl halide leads in a metal-mediated reaction and under suitable conditions (base, exclusion of oxygen) to the aryl- and heteroaryl ketones 3. Preferred metal reagents are palladium catalysts.

borohydride/trifluoroacetic acid, to the corresponding the β-amino-ester. The amino group is then converted to the tert-butyl carbamate and the ester group hydrolyzed using a base, preferably potassium or sodium hydroxide in a water/tetrahydrofuran mixture, to yield the acid 7. The 2α,3β,11bβ isomer of 7 is the predominant product and is easily separated from the other possible diastereomers, e. g., by crystallization.

Acid 7 is elaborated into amine 8 via a Curtius rearrangement. A preferred protocol for this conversion is a two-step sequence, where the acid is first heated with a mixture of diphenylphosphoryl azide, a base (e. g., triethylamine), and 2-(trimethylsilyl)-ethanol, in a solvent such as toluene, at about 70-110 °C. The 2-(trimethylsilyl)-ethyl carbamate intermediate is then deprotected with a fluoride, e. g., tetrabutylammonium fluoride in THF, at about 50 °C (*Tetrahedron Lett.* 1984, *25*, 3515).

Reaction of amine 8 with an appropriately substituted 2,5-dimethoxytetrahydrofuran in acetic acid/pyridine (*J. Org. Chem.* 1998, *63*, 6715) at about 100 °C produces 9, which is converted to the final compound of formula 10, using methods known in the art.

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

As described above, the compounds of formula (I) of the present invention can be used as medicaments for the treatment and/or prophylaxis of diseases which are associated with DPP-IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome or β-cell protection, preferably non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Furthermore, the compounds of the present invention can be used as diuretic agents or for the treatment and/or prophylaxis of hypertension.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

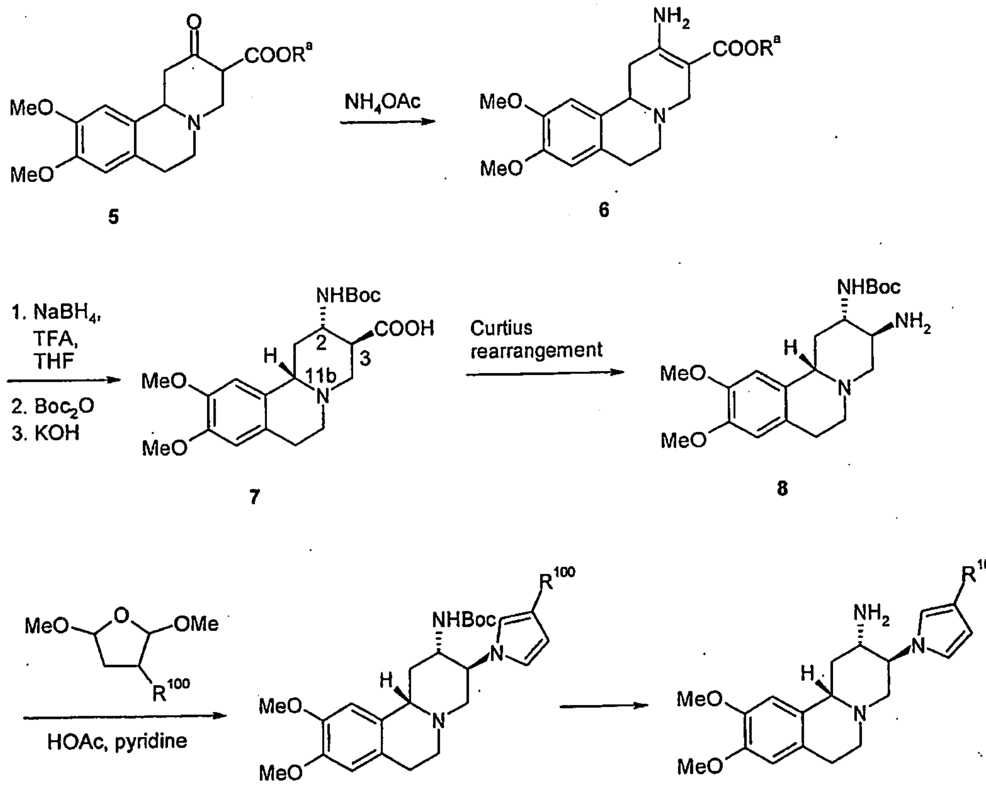
Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with DPP-IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome or β-cell protection, preferably for use as therapeutic active substances for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose

The ketones are then converted to amino functions by known methods. One possibility is the conversion of the keto group to an oxime of formula 3 using hydroxylamine hydrochloride and sodium acetate in a solvent such as ethanol. Oximes can be reduced by e.g. catalytic hydrogenation to the final compounds 4.

The 2α, 3β, 11bβ isomer is usually the predominant product which is easily separated from the other stereoisomer by chromatography.

The separation of the enantiomeric mixture in its chiral components can be achieved by chromatography on a chiral phase.

Scheme 2



R^a = methyl or ethyl; R^{100} = R^{10} or C(O)–R^{101}, with R^{101} = H, lower alkyl, or halogenated lower alkyl.

The synthesis of pyrrol-1-yl derivatives 10 is outlined in Scheme 2 and starts with the β-ketoester 5 (R^a = methyl or ethyl), a compound well known in the art (*Helv. Chim.Acta* 1958, *41*, 119). Reaction of 5 with ammonium acetate in a solvent such as methanol produces the β-enamino-ester 6, which is reduced, preferably with sodium

tolerance. Furthermore, the invention relates to compounds as defined above for use as diuretic agents or for use as therapeutic active substances for the treatment and/or prophylaxis of hypertension.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with DPP-IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome or β-cell protection, preferably for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance, which method comprises administering a compound as defined above to a human being or animal. Furthermore, the invention relates to a method for the treatment and/or prophylaxis as defined above, wherein the disease is hypertension or wherein a diuretic agent has a beneficial effect.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with DPP-IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome or β-cell protection, preferably for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Furthermore, the invention relates to the use as defined above, wherein the disease is hypertension or to the use as diuretic agent.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with DPP-IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome or β-cell protection, preferably for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Such medicaments comprise a compound as defined above. Furthermore, the invention relates to the use as defined above, wherein the disease is hypertension or the use for the preparation of diuretic agents.

In context with the methods and uses defined above, the following diseases relate to a preferred embodiment: diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, obesity, and/or metabolic syndrome or β-cell protection, preferably non-insulin dependent diabetes mellitus and/or impaired glucose tolerance.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the Examples or by analogous methods. Appropriate reaction

conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below or in the Examples or by methods known in the art.

The following tests were carried out in order to determine the activity of the compounds of formula I.

Activity of DPP-IV inhibitors are tested with natural human DPP-IV derived from a human plasma pool or with recombinat human DPP-IV. Human citrate plasma from different donors is pooled, filterted through a 0.2 micron membrane under sterile conditions and aliquots of 1 ml are shock frozen and stored at -120 °C until used. In the colorimetric DPP-IV assay 5 to 10 µl human plasma and in the fluorometric assay 1.0 µl of human plasma in a total assay volume of 100 µl is used as an enzyme source. The cDNA of the human DPP-IV sequence of amino acid 31 - to 766, restricted for the N-terminus and the transmembrane domain, is cloned into Pichia pastoris. Human DPP-IV is expressed and purified from the culture medium using conventional column chromatography including size exclusion and anion and cation chromatography. The purity of the final enzyme preparation of Coomassie blue SDS-PAGE is > 95 %. In the colorimetric DPP-IV assay 20 ng rec.-h DPP-IV and in the fluorometric assay 2 ng rec-h DPP-IV in a total assay volume of 100 µl is used as an enzyme source.

In the fluorogenic assay Ala-Pro-7-amido-4-trifluoromethylcoumarin (Calbiochem No 125510) is used as a substrate. A 20 mM stock solution in 10 % DMF/H_2O is stored at -20 °C until use. In IC_{50} determinations a final substrate concentration of 50 µM is used. In assays to determine kinetic parameters as K_m, V_{max}, K_i, the substrate concentration is varied between 10 µM and 500 µM.

In the colorimetric assay H-Ala-Pro-pNA.HCl (Bachem L-1115) is used as a substrate. A 10 mM stock solution in 10% MeOH/H2O is stored at –20 °C until use. In IC_{50} determinations a final substrate concentration of 200 µM is used. In assays to determine kinetic parameters as K_m, V_{max}, K_i, the substrate concentration is varied between 100 µM and 2000 µM.

Fluorescence is detected in a Perkin Elmer Luminescence Spectrometer LS 50B at an excitation wavelength of 400 nm and an emission wavelength of 505 nm continuously every 15 seconds for 10 to 30 minutes. Initial rate constants are calculated by best fit linear regression.

The absorption of pNA liberated from the colorimetric substrate is detected in a Packard SpectraCount at 405 nm continuosly every 2 minutes for 30 to 120 minutes. Initial rate constants are calculated by best fit linear regression.

DPP-IV activity assays are performed in 96 well plates at 37 °C in a total assay volume of 100 µl. The assay buffer consists of 50 mM Tris/HCl pH 7.8 containing 0.1 mg/ml BSA and 100 mM NaCl. Test compounds are solved in 100 % DMSO, diluted to the desired concentration in 10% DMSO/H_2O. The final DMSO concentration in the assay is 1 % (v/v). At this concentration enzyme inactivation by DMSO is < 5%. Compounds are with (10 minutes at 37 °C) and without preincubation with the enzyme. Enzyme reactions are started with substrate application followed by immediate mixing.

IC_{50} determinations of test compounds are calculated by non-linear best fit regression of the DPP-IV inhibition of at least 5 different compound concentrations. Kinetic parameters of the enzyme reaction are calculated at at least 5 different substrate concentrations and at least 5 different test compound concentrations.

The compounds of the present invention exhibit IC_{50} values of 0.1 nM to 10 µM, more preferably of 0.1 - 100 nM, as shown in the following table:

Example	IC_{50} [µM]
2	0.029
9	0.0115
30	0.005
33	0.0054
35	0.0042

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

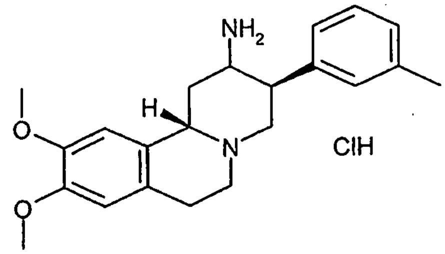
The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples:

Example 1

rac-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ylamine hydrochloride



a) *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-one

Palladium acetate (21 mg, 0.01 mmol), sodium tert-butoxide (276 mg, 2.87 mmol), and tri-tert-butylphosphine (23 mg, 0.115 mmol) were dissolved under argon in tetrahydrofuran (2 mL). 3-Bromotoluene (164 mg, 0.957 mmol) and *rac*-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-benzo[a]quinolizin-2-one (250 mg, 0.957 mmol) were sequentially added under flow of argon and stirred at room temperature for 12 hours. The reaction mixture was diluted with water and extracted 3 times with ether. The combined organic layers were washed with water, brine, and dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product. The crude product was chromatographed on silica gel (ether) to afford 139 mg (0.39 mmol, 41 %) of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one as a light yellow solid.

MS (ISP): 343.3 $(M+H)^+$.

^1H NMR ($CDCl_3$) : δ = 7.29-7.24 (m, 1 H), 6.99-6.73 (m, 2 H), 6.62 (s, 1 H), 6.59 (s, 1 H), 3.96-3.92 (m, 1 H), 3.89-3.80 (m, 6 H, 2 methoxy groups), 3.76-3.72 (m, 1 H), 3.43-3.38 (m, 1 H), 3.19-3.93 (m, 5 H), 2.79-2.64 (m, 3 H), 2.32 (s, 3 H, Ar-CH_3).

b) *rac*-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-ylamine hydrochloride

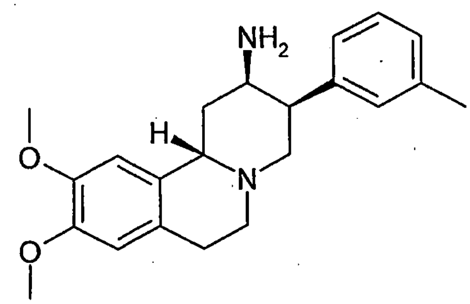
rac-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (62 mg), NaOAc (16 mg) and hydroxylamine hydrochloride (14 mg) were dissolved in ethanol (2 ml) and stirred at room temperature for 3 hours. Water (2 ml) and Ni-Al alloy (100 mg) were added. NaOH as a 32% aqueous solution (0.35 ml) was

added dropwise to this suspension. Hydrogen evolved and the reaction mixture turned warm. The reaction mixture was stirred at room temperature over night. The same amount of base and Ni-Al alloy was added and the reaction was stirred at room temperature for further 3 hours. The reaction mixture was filtered and the solution extracted 3 times with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH aq 25% 100/5/1) afforded the product as a mixture of the cis-and the trans-diastereoisomers. The amines were dissolved in methylene chloride and HCl in ether was added. The solvent was evaporated to leave the product (46 mg, 67 %) as an orange solid.

MS (ISP): 353.3 $(M+H)^+$.

Example 2

rac-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine



a) *rac*-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one

A mixture of palladium acetate (1.72 g), sodium tert-butoxide (22.01 g) and *rac*-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-benzo[a]quinolizin-2-one (20.0 g) [D. Beke, C. Szantay, Chem. Ber. 95, 2132 (1962)] were evaporated under high vacuum at 80 °C and charged with argon three to five times. Degassed tetrahydrofuran (220 mL) was added at room temperature under argon. The reaction mixture was stirred for 15 minutes at room temperature, and tri-tert-butylphosphine (1.86 g) and 3-bromotoluene (13.75 g) were added simultaneously with a syringe. The reaction mixture was stirred at 20-25 °C under argon for 4 hours. The crude reaction mixture was poured on ice/water (1 L), and the precipitate was filtered off. The filtrate was extracted twice with tert-butylmethyl ether. The organic phase was concentrated, the residue was combined with the precipitate obtained above and dissolved in methylene chloride, washed with water and brine. The organic layer was dried over magnesium sulfate and filtered. The solvent was evaporated.

The residue was purified by column chromatography (silica gel, 325 g) using methylene chloride/ethyl acetate 1:1 as eluent to yield *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (11.9 g) as a light yellow solid.

MS (ISP): 352.4 $(M+H)^+$.

b) *rac*-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one oxime

To a suspension of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (26.95 g) in ethanol (500 mL) were added hydroxylamine hydrochloride (5.82 g) and sodium acetate (6.92 g). The reaction mixture was stirred at room temperature for 4.5 hours, cold water (1.5 L) was added. The precipitate was filtered off, and the cake was washed with cold water and dried over P_2O_5 under high vacuum over night to obtain *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one oxime (26.48 g) as a colourless solid.

MS (ISP): 367.4 $(M+H)^+$.

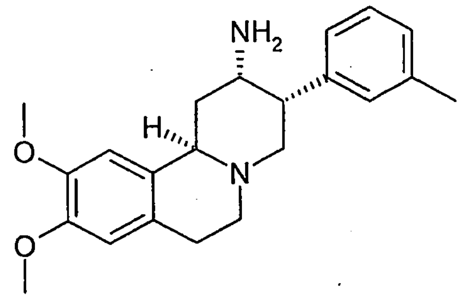
c) *rac*-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

To a solution of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one oxime (30.2 g) in ethanol/dioxane 1:1 (2400 mL) was added the wet Ra/Ni (150 g). The reaction mixture was evaporated and charged with hydrogen, conc. NH_4OH (45 mL) was added with the help of a syringe, and the hydrogenation was started. After 4.5 hours at 1.1 bar and room temperature, the reaction mixture was filtered over a fine filter (caution!), the catalyst was washed with ethanol, the filtrate concentrated. The residue was chromatographed over silica gel using methylene chloride/methanol/conc. ammonia 95:5:0.5 and 90:10:0.9 as eluent to obtain the title compound (3.0 g) as a yellow powder. This product was eluted first during chromatography.

MS (ISP): 353.4 $(M+H)^+$.

Example 3

9,10-Dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2(S)-ylamine

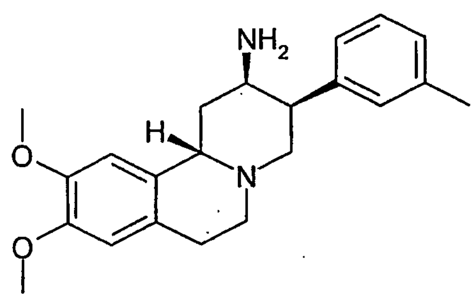


The title compound was obtained after separation of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine (Example 2) through a Chiralpak AD column with 15 % ethanol/heptane as eluent. The retention time was 115 minutes.

MS (ISP): 353.3 $(M+H)^+$, $[\alpha]_D$ +156 ° (c 0.558, chloroform).

Example 4

9,10-Dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine

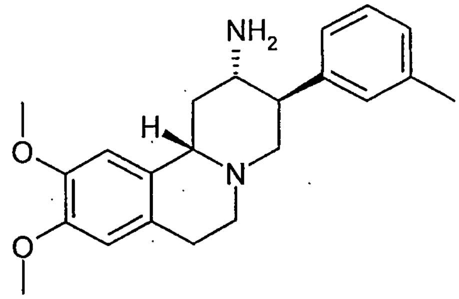


The title compound was obtained after separation of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine (Example 2) through a Chiralpak AD column with 15 % ethanol/heptane as eluent. The retention time was 159 minutes.

MS (ISP): 353.3 $(M+H)^+$, $[\alpha]_D$ −154 ° (c 0.523, chloroform).

Example 5

rac-9,10-Dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

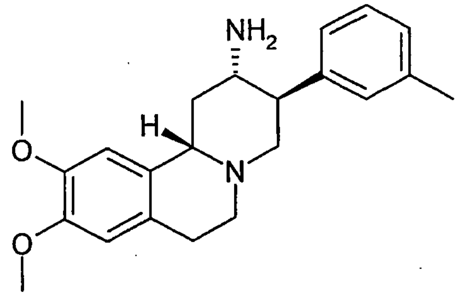


The product was obtained in the final chromatography described in Example 2 eluting as second compound (20.2 g) as light yellow crystals.

MS (ISP): 353.4 $(M+H)^+$.

Example 6

9,10-Dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine

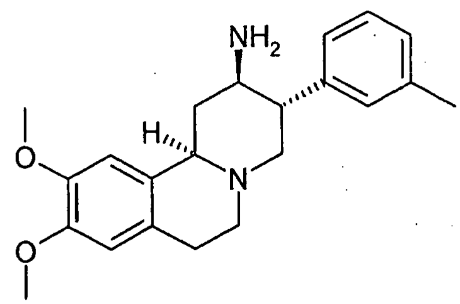


The title compound was obtained after separation of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine (Example 5) through a Chiralpak AD column with 20 % isopropanol/heptane as eluent. The retention time was 270 minutes.

MS (ISP): 353.4 $(M+H)^+$, $[\alpha]_D$ −57 ° (c 0.345, chloroform).

Example 7

9,10-Dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine

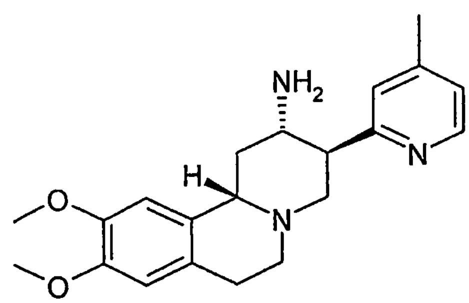


The title compound was obtained after separation of *rac*-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine (Example 5) through a Chiralpak AD column with 20 % isopropanol/heptane as eluent. The retention time was 158 minutes.

MS (ISP): 353.4 $(M+H)^+$, $[\alpha]_D$ +57 ° (c 0.545, chloroform).

Example 8

rac-9,10-Dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

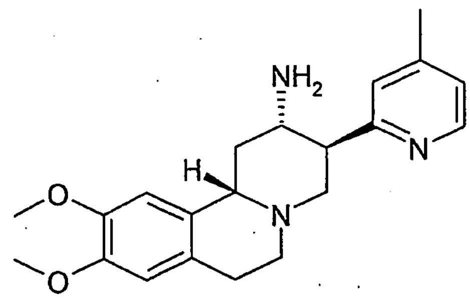


The title compound was prepared in analogy to Example 2. It was obtained as an orange-red powder. This product was eluted second during chromatography (cf. Example 15).

MS (ISP): 354.3 $(M+H)^+$.

Example 9

9,10-Dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine

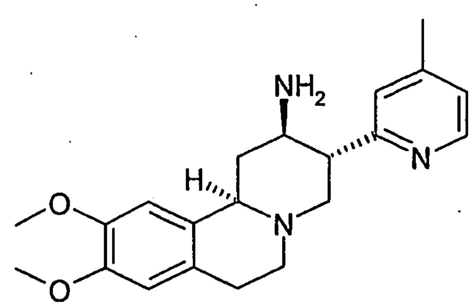


The title compound was obtained after separation of *rac*-9,10-Dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine (Example 8) through a Chiralpak AD column with 20 % isopropanol/heptane as eluent. The retention time was 350 minutes.

MS (ISP): 354.3 $(M+H)^+$, $[\alpha]_D$ −67.5 ° (c 0.527, chloroform).

Example 10

9,10-Dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine

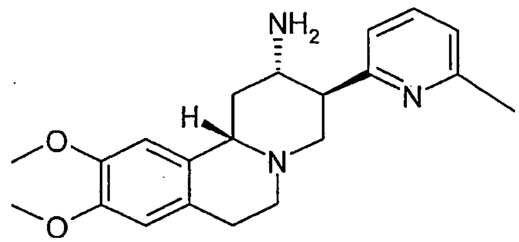


The title compound was obtained after separation of *rac*-9,10-Dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine (Example 8) through a Chiralpak AD column with 20 % isopropanol/heptane as eluent. The retention time was 200 minutes.

MS (ISP): 354.3 $(M+H)^+$, $[\alpha]_D$ +68.8 ° (c 0.520, chloroform).

Example 11

rac-9,10-Dimethoxy-3β-(6-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine.

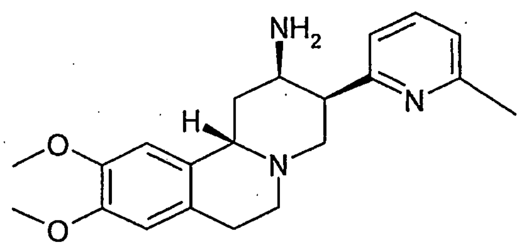


The title compound was prepared in analogy to Example 2. It was obtained as a yellow powder. This product was eluted second during chromatography (cf. Example 12).

MS (ISP): 354.4(M+H)$^+$.

Example 12

rac-9,10-Dimethoxy-3β-(6-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

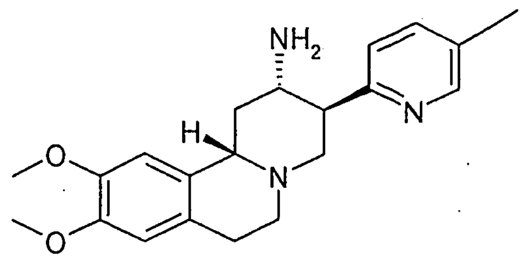


The title compound was prepared in analogy to Example 2. It was obtained as a yellow powder. This product was eluted first during chromatography (cf. Example 11).

MS (ISP): 354.4 (M+H)$^+$.

Example 13

rac-9,10-Dimethoxy-3β-(5-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine.

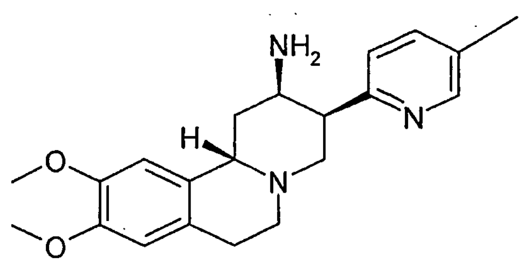


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 14).

MS (ISP): 354.3 $(M+H)^+$.

Example 14

rac-9,10-Dimethoxy-3β-(5-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine.

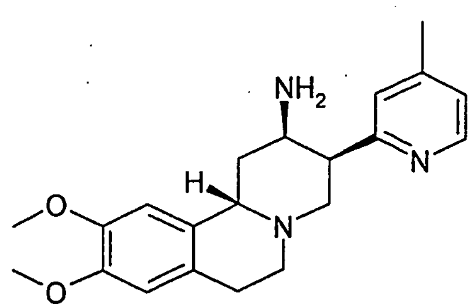


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 13).

MS (ISP): 354.3 $(M+H)^+$.

Example 15

rac-9,10-Dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

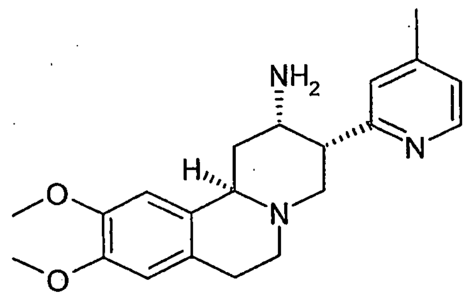


The title compound was prepared in analogy to Example 2. It was obtained as an orange powder. This product was eluted first during chromatography (cf. Example 8).

MS (ISP): 354.3 $(M+H)^+$.

Example 16

9,10-Dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine

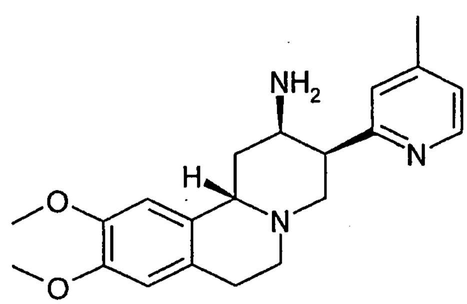


The title compound was obtained after separation of *rac*-9,10-Dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine (Example 15) through a Chiralpak AD column with 20 % ethanol/heptane as eluent. The retention time was 200 minutes.

MS (ISP): 354.3 $(M+H)^+$, $[\alpha]_D$ +129 ° (c 0.511, chloroform).

Example 17

9,10-Dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine

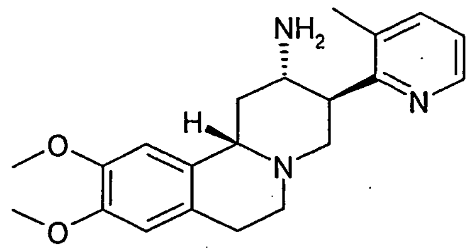


The title compound was obtained after separation of *rac*-9,10-Dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine (Example 15) through a Chiralpak AD column with 20 % ethanol/heptane as eluent. The retention time was 159 minutes.

MS (ISP): 354.3 $(M+H)^+$, $[\alpha]_D$ –127 ° (c 0.597, chloroform).

Example 18

rac-9,10-Dimethoxy-3β-(3-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine.

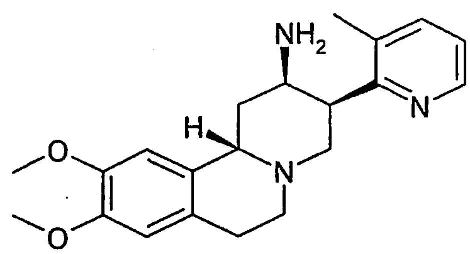


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 19).

MS (ISP): 354.3 $(M+H)^+$.

Example 19

rac-9,10-Dimethoxy-3β-(3-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

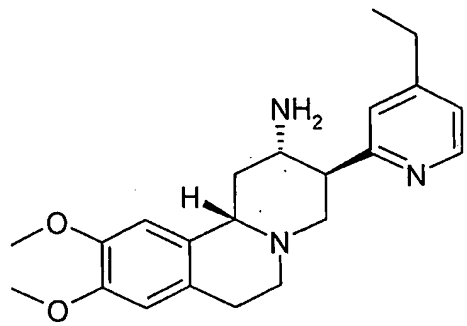


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 18).

MS (ISP): 354.3 $(M+H)^+$.

Example 20

rac-3β-(4-Ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

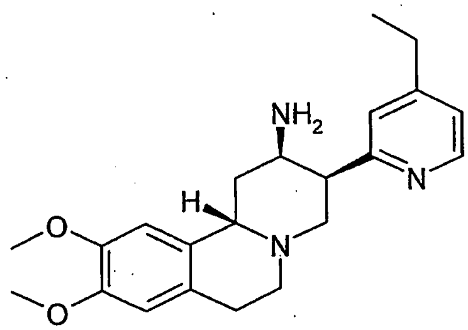


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 21).

MS (ISP): 368.1 $(M+H)^+$.

Example 21

rac-3β-(4-Ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

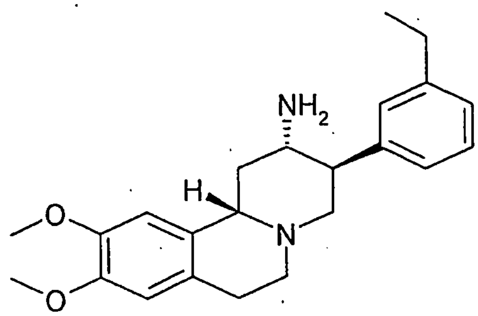


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 20).

MS (ISP): 368.1 $(M+H)^+$.

Example 22

rac-3β-(4-Ethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

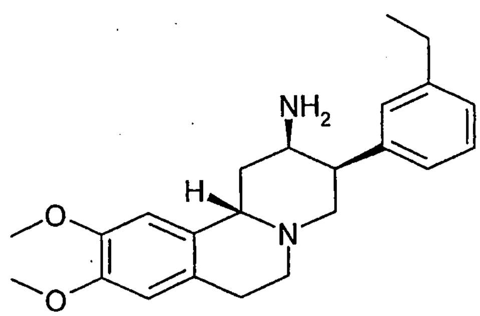


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 23).

MS (ISP): 367.4 $(M+H)^+$.

Example 23

rac-3β-(4-Ethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

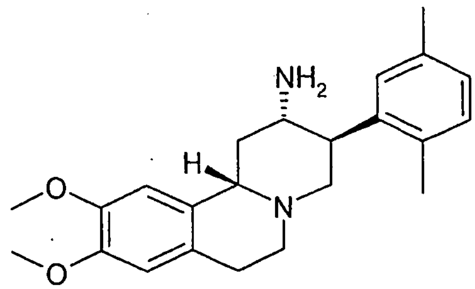


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 22).

MS (ISP): 367.4 $(M+H)^+$.

Example 24

rac-3β-(2,5-Dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

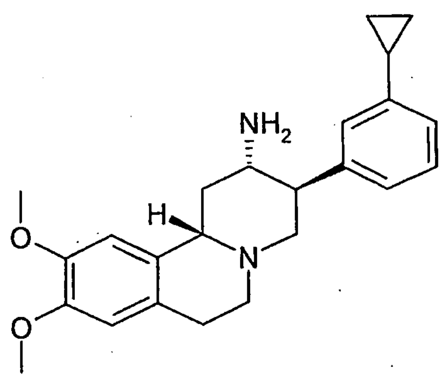


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 27).

MS (ISP): 367.4 $(M+H)^+$.

Example 25

rac-3β-(3-Cyclopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

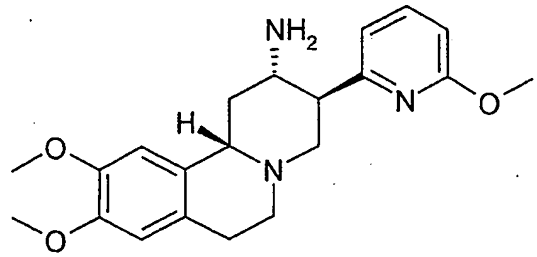


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 29).

MS (ISP): 379.3 $(M+H)^+$.

Example 26

rac-3β-(6-Methoxy-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

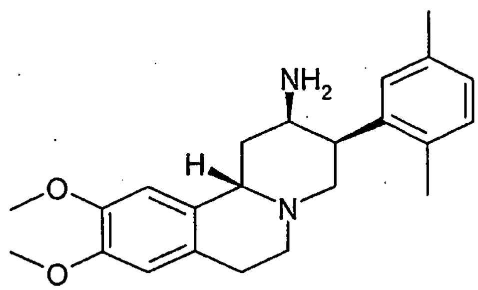


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder.

MS (ISP): 370.4 $(M+H)^+$.

Example 27

rac-3β-(2,5-Dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

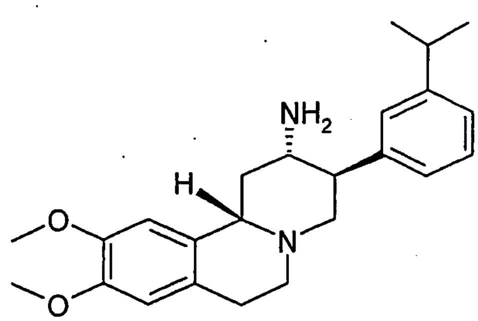


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 24).

MS (ISP): 367.3 $(M+H)^+$.

Example 28

rac-3β-(3-Isopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

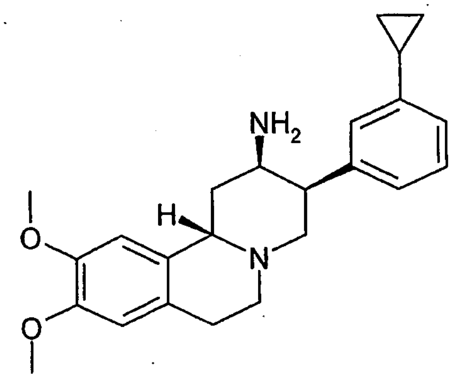


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder.

MS (ISP): 381.4 $(M+H)^+$.

Example 29

rac-3β-(3-Cyclopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

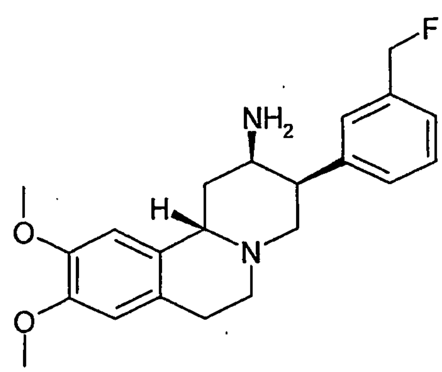


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 25).

MS (ISP): 379.4 $(M+H)^+$.

Example 30

rac-3β-(3-Fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine

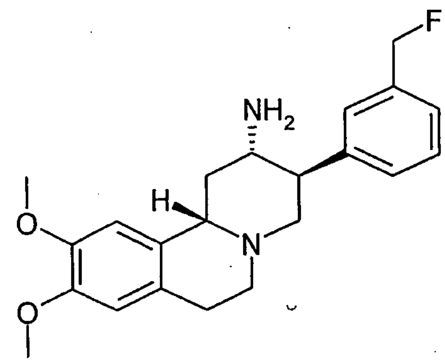


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted first during chromatography (cf. Example 31).

MS (ISP): 371.4 $(M+H)^+$.

Example 31

rac-3β-(3-Fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

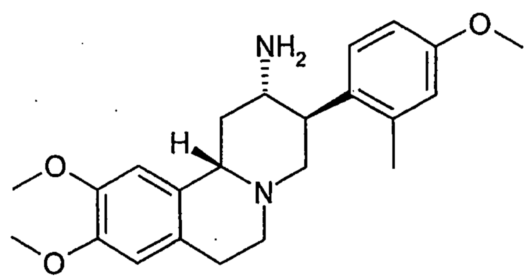


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder. This product was eluted second during chromatography (cf. Example 30).

MS (ISP): 371.3 $(M+H)^+$.

Example 32

rac-3β-(4-Methoxy-2-methyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

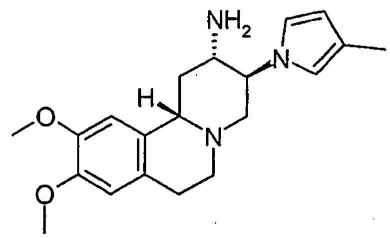


The title compound was prepared in analogy to Example 2. It was obtained as an off white powder.

MS (ISP): 383.4 $(M+H)^+$.

Example 33

rac-9,10-Dimethoxy-3β-(3-methyl-pyrrol-1-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine



a) 2-Amino-9,10-dimethoxy-1,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline-3-carboxylic acid ethyl ester

A mixture of 9,10-dimethoxy-2-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinoline-3-carboxylic acid ethyl ester (*Helv. Chim. Acta* 1958, *41*, 119; 4.00 g, 12.0 mmol) and ammonium acetate (13.9 g, 180 mmol) in methanol was stirred 5 h at room temperature. After evaporation of the solvent the residue was partitioned between dichloromethane and 1 M aq. sodium hydroxide solution. The organic layer was dried ($MgSO_4$), and triturated with heptane to afford the title compound (3.71 g, 93%). Off-white solid, MS (ISP) 333.2 $(M+H)^+$.

b) *rac*-2α-tert-Butoxycarbonylamino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinoline-3β-carboxylic acid ethyl ester

Trifluoroacetic acid (120 mL) was added at 0°C to a solution of 2-amino-9,10-dimethoxy-1,6,7,11b-tetrahydro-4H-pyrido[2,1-a]isoquinoline-3-carboxylic acid ethyl ester (6.90 g, 20.8 mmol) in tetrahydrofuran (60 mL), then after 30 min the homogeneous solution was treated with sodium borohydride (1.64 g, 41.5 mmol) and stirred for another 40 min. The reaction mixture was concentrated in vacuo and the residue partitioned between 2 M aq. sodium hydroxide solution and dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane (80 mL), and a solution of di-tert-butyl-dicarbonate (4.98 g, 22.8 mmol) in dichloromethane (50 mL) was added at room temperature. The solution was stirred overnight at room temperature, concentrated, and the residue was triturated in heptane to afford the title compound (7.44 g, 83%). Light yellow solid, MS (ISP) 435.4 $(M+H)^+$.

c) *rac*-2α-tert-Butoxycarbonylamino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinoline-3β-carboxylic acid

Potassium hydroxide (86%, 4.47 g, 68.5 mmol) was added to a suspension of *rac*-2α-tert-butoxycarbonylamino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinoline-3β-carboxylic acid ethyl ester (7.44 g, 17.1 mmol) in tetrahydrofuran (70 mL) and water (70 mL). After heating 5 h at reflux, the mixture was concentrated in vacuo. The residue was taken up in 1M aq. potassium phosphate buffer (pH 6.85) and dichloromethane, and ethanol was added until a clear two-phase mixture was obtained. The organic layer was separated, washed with brine and evaporated to afford the title compound (6.91 g, 99%). Light yellow solid, MS (ISN) 405.3 $(M-H)^-$.

d) *rac*-(2α-tert-Butoxycarbonylamino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-3β-yl)-carbamic acid 2-trimethylsilanyl-ethyl ester

A mixture of *rac*-2α-tert-butoxycarbonylamino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinoline-3β-carboxylic acid (6.91 g, 17.0 mmol), diphenylphosphoryl azide (7.40 g, 25.6 mmol), triethylamine (1.72 g, 17.0 mmol), 2-(trimethylsilyl)-ethanol (30.2 g, 256 mmol) and toluene (40 mL) was heated 48 h at 80 °C under a gentle nitrogen stream. The reaction mixture was then concentrated in vacuo and the residue chromatographed (SiO_2, CH_2Cl_2/MeOH/NH_4OH 80:1:0.2), and the product fractions triturated in hexane/ethyl acetate 1:1 to afford the title compound (5.22 g, 59%). White solid, MS (ISP) 522.4 $(M+H)^+$.

e) *rac*-(3β-Amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl)-carbamic acid tert-butyl ester

A suspension of *rac*-(2α-tert-butoxycarbonylamino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-3β-yl)-carbamic acid 2-trimethylsilanyl-ethyl ester (5.22 g, 10.0 mmol) in tetrabutylammonium fluoride solution (1 M in THF, 42 mL, 42 mmol) was heated 90 min at 50 °C. The resultant solution was concentrated in vacuo and chromatographed (CH_2Cl_2/MeOH/NH_4OH 95:5:0.25) to afford the title compound (3.59 g, 95%). Light yellow solid, MS (ISP) 378.4 $(M+H)^+$.

f) *rac*-[3β-(3-Formyl-pyrrol-1-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydroα-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester

2,5-dimethoxytetrahydrofuran-3-carbaldehyde (73 mg, 0.41 mmol) was added to a solution of *rac*-(3β-amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl)-carbamic acid tert-butyl ester (140 mg, 0.37 mmol) in acetic acid (1.7 mL, 29 mmol) and pyridine (1.05 mL, 13 mmol). The homogeneous solution was

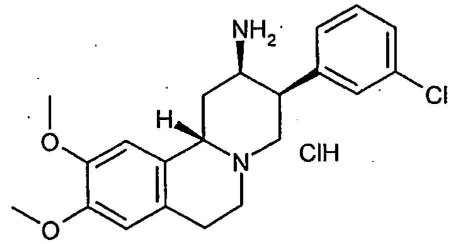
heated at 100 °C for 90 min, then evaporated, and the residue was chromatographed (SiO_2, heptane/ethyl acetate gradient) to afford the title compound (75 mg, 44%). White solid, MS (ISP) 456.3 $(M+H)^+$.

g) *rac*-9,10-Dimethoxy-3β-(3-methyl-pyrrol-1-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine

rac-[3β-(3-Formyl-pyrrol-1-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester (75 mg, 0.17 mmol) was dissolved in trifluoroacetic acid (1 mL) cooled to 0 °C, treated with triethylsilane (55 mg, 0.46 mmol), stirred at 0 °C for 1 h, and concentrated in vacuo. Chromatography of the residue (SiO_2, $CH_2Cl_2/MeOH/NH_4OH$ 95:5:0.25) produced the title compound (48 mg, 85%). White solid, MS (ISP) 342.2 $(M+H)^+$.

Example 34

rac-3β-(3-Chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine hydrochloride



a) *rac*-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one

The ketone was obtained as described in example 1a) using 1,3-dichloro-benzene as a light yellow solid (40 mg, 11 %).

MS (ISP): 372.2 $(M+H)^+$.

^1H NMR ($CDCl_3$) : δ = 7.38-7.06 (m, 4 H), 6.64 (s, 1 H), 6.59-6.58 (m, 1 H), 4-3.7 (m, 8 H), 3.5-3.35 (m, 1 H), 3.2-2.6 (m, 7 H).

b) *rac*-3β-(3-Chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine hydrochloride

rac-3β-(3-Chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (60 mg, 0.16 mmol) was dissolved in methanol (10 ml) and methylene chloride (5 ml). Ammonium acetate (248 mg, 3.2 mmol) was added and the

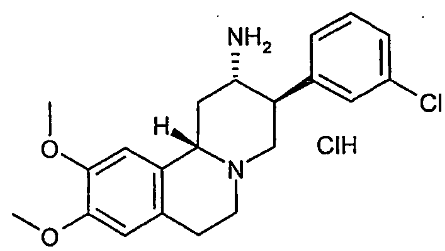
reaction was stirred at room temperature over night. Sodium cyanoborohydride (13 mg, 0.2 mmol) was added. After stirring for one hour at room temperature the reaction mixture was diluted with water and extracted 3 times with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (CH2Cl2/MeOH/25% aq NH3 = 97/3/0.5) to afford the product eluting first as one of the diastereomers. It was dissolved in diethyl ether and HCl in ether was added. The solvent was evaporated to leave the product as a light yellow solid (22 mg, 33 %).

MS (ISP): 372.3 $(M+H)^+$.

^{1}H NMR ($CDCl_3$) : δ = 7.4-7.10 (m, 4 H), 6.69 (s, 1 H), 6.62 (s, 1 H), 3.9-3.7 (m, 6 H), 3.6-2.35 (m, 10 H), 2-1.9 (m, 1 H). ISP-MS : m/z = 373.3 (M+H).

Example 35

rac-3β-(3-Chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride



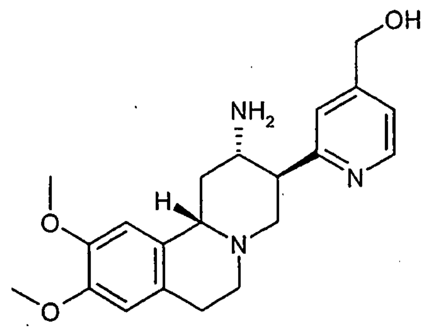
The product was obtained in the final chromatography described in Example 1b) eluting as second compound. The product was dissolved in diethyl ether and 1N HCl in diethyl ether was added. The solvent was evaporated to leave the product as a light yellow solid (26 mg).

MS (ISP): 373.3 $(M+H)^+$.

^{1}H NMR ($CDCl_3$) : δ = 7.31-7.15 (m, 4 H), 6.73 (s, 1 H), 6.60 (s, 1 H), 3.9-3.8 (m, 7 H), 3.4-2.2 (m, 9 H).

Example 36

rac-[2-(2α-Amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a] isoquinolin-3β-yl)-pyridin-4-yl]-methanol



a) 2-Bromo-4-(tert-butyl-dimethyl-silanyloxymethyl)-pyridine

To a solution of 2-bromo-4-(hydroxymethyl)pyridine (Lancaster, [CAS 118289-16-0]) (7.3 g) and imidazole (2.65 g) in dichloromethane (80 ml) was added dropwise over 15 minutes at 0-5 °C a solution of tert-butyldimethylsilyl chloride (5.85 g) in dichloromethane (20 ml). The reaction mixture was stirred at 0-5 °C for 3h, poured onto ice/water and extracted with dichloromethane. The organic phase was washed with water, sat. sodiumhydrogencarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude compound was filtered over silica gel (200 g) with dichloromethane as eluent. The product containing fractions were evaporated to dryness to obtain 2-bromo-4-(tert-butyl-dimethyl-silanyloxymethyl)-pyridine (10.3 g) as a colourless liquid.

MS (ISP): 302.0, 304.1 $(M+H)^+$.

b) *rac*-3β-[4-(tert-Butyl-dimethyl-silanyloxymethyl)-pyridin-2-yl]-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one

A mixture of palladium acetate (0.84 g), sodium tert-butoxide (9.8 g) and *rac*-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-benzo[a]quinolizin-2-one (8.90 g) [D. Beke, C. Szantay, Chem. Ber. 95, 2132 (1962)] was evaporated under high vacuum at 80 °C and flushed with argon three to five times. Degassed tetrahydrofuran (200 ml) was added at room temperature under argon. The reaction mixture was stirred for 15 minutes at room temperature, and tri-tert-butylphosphine (0.76 g) and 2-bromo-4-(tert.-butyl-dimethyl-silanyloxymethyl)-pyridine (10.3 g) were added simultaneously with a syringe. The reaction mixture was stirred at 20-25 °C under argon for 18 hours. The crude reaction mixture was poured on ice/water (1 l), neutralized with 2N hydrochloric acid and extracted with tert.-butylmethyl ether. The organic phase was washed with water and

brine, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (silica gel, 400 g) using cyclohexane/ethyl acetate 1:1 as eluent to yield *rac*-3β-[4-(tert-butyl-dimethyl-silanyloxymethyl)-pyridin-2-yl]-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one (6.9 g) as a yellow foam.

MS (ISP): 483.4 $(M+H)^+$.

c) *rac*-3β-(4-Hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one

To a solution of *rac*-3β-[4-(tert.-butyl-dimethyl-silanyloxymethyl)-pyridin-2-yl]-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one (6.85 g) in tetrahydrofuran (340 ml) was added tetrabutylammonium fluoride trihydrate (11.2 g). The reaction mixture was stirred at room temperature for 2h and concentrated. To the residue was added water/ice, and it was extracted with dichloromethane. The organic phase was washed with water and brine, dried over magnesium sulphate and concentrated. The residue was purified by chromatography on silica gel using dichloromethane/methanol/ammonium hydroxide as eluent to obtain *rac*-3β-(4-hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one (4.6 g) as a yellow amorphous powder.

MS (ISP): 369.1 $(M+H)^+$

d) *rac*-3β-(4-Hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one oxime.

This compound was prepared in analogy to example 2b starting from *rac*-3β-(4-hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one (4.6 g), hydroxylamine hydrochloride (0.954 g) and sodium acetate (1.12 g) in ethanol (140 ml) to obtain *rac*-3β-(4-hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one oxime (4.67 g) as light yellow crystals.

MS (ISP): 384.3 $(M+H)^+$

e) *rac*-[2-(2α-Amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a] isoquinolin-3β-yl)-pyridin-4-yl]-methanol

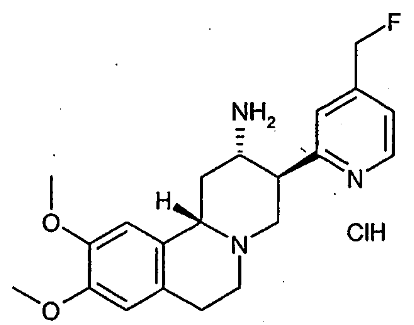
This compound was prepared in analogy to example 2c starting from *rac*-3β-(4-hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-pyrido[2,1-a]isoquinolin-2-one oxime (4.60 g), to obtain after chromatography on silica gel with dichloromethane/methanol/ammonium hydroxide *rac*-[2-(2α-amino-9,10-dimethoxy-

1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-3β-yl)-pyridin-4-yl]-methanol (2.16 g) as a light yellow solid.

MS (ISP): 370.3 $(M+H)^+$

Example 37

rac-3β-(4-Fluormethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride



a) [*rac*-3β-(4-Hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester

To a solution of *rac*-[2-(2α-amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-3β-yl)-pyridin-4-yl]-methanol (2.15 g) in dichloromethane (215 ml) was added di-tert.-butyl dicarbonate (1.27 g). The reaction mixture was refluxed for 2h, concentrated, and the residue was purified by chromatography on silica gel using dichloromethane/methanol/ammonium hydroxide as eluent to obtain [*rac*-3β-(4-hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ- hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester (2.35 g) as light yellow solid.

MS (ISP): 470.3 $(M+H)^+$

b) [*rac*-3β-(4-Fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester.

To a solution of [*rac*-3β-(4-hydroxymethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ- hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester (0.5 g) in dichloromethane (15 ml) was added at 0 °C diethylaminosulfur-trifluoride (0.515 g). The reaction mixture was stirred at 0-5 °C for 2h, quenched with ice/bicarbonate, extracted with dichloromethane. The organic phase was washed with brine, dried over magnesium sulphate and concentrated. The residue was purified by

chromatography on silica gel (50 g) with dichloromethane/methanol 2, 4 and 8 % as eluent to obtain [*rac*-3β-(4-fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester (0.15 g) as a yellow foam.

MS (ISP): 472.4 $(M+H)^+$

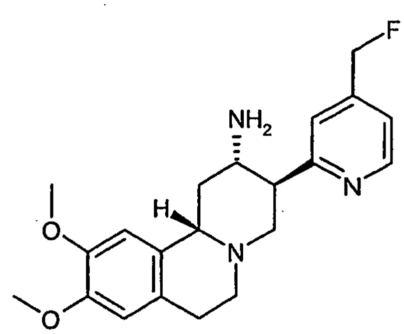
c) *rac*-3β-(4-Fluormethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride

To a solution of [*rac*-3β-(4-fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-yl]-carbamic acid tert-butyl ester (0.095 g) in dioxane (5.0 ml) was added 4 molar HCl/dioxane (5.0 ml). The reaction mixture was stirred over night at room temperature, and diethyl ether (75 ml) was added to precipitate the hydrochloride. The crystals were filtered, washed with ether and dried to obtain the title compound (0.065 g) as a light yellow solid.

MS (ISP): 372.1 $(M+H)^+$

Example 38

rac-3β-(4-Fluormethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine.



A solution of *rac*-3β-(4-fluormethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride (0.040 g) in methanol/water 1:1 (5 ml) was filtrated over basic ion exchange resin (IRA-400) using the same solvent as eluent. The product fractions were combined and evaporated to dryness to obtain the title compound (0.025 g) as orange foam.

MS (ISP): 372.1 $(M+H)^+$

Galenical Examples

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Ingredients	
Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

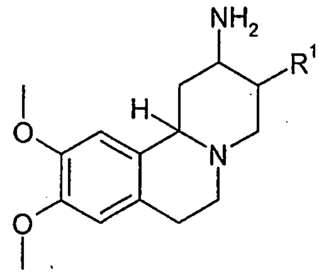
Sachets containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	
Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesium stearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavouring additives and filled into sachets.

Claims

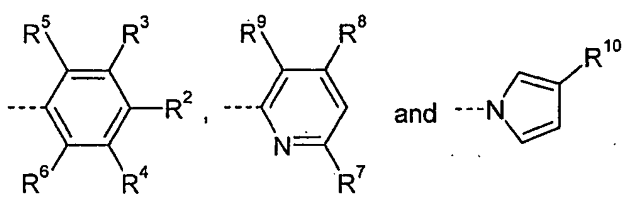
1. Compounds of formula (I)



(I)

wherein

R^1 is selected from



R^2 is hydrogen or lower alkoxy;

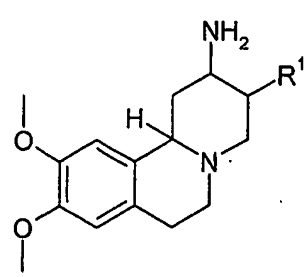
R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, lower alkyl, halogenated lower alkyl, halogen or cycloalkyl; provided that R^2, R^3, R^4, R^5 and R^6 are not all hydrogen;

R^7, R^8 and R^9 are each independently hydrogen, lower alkyl, lower alkoxy, lower hydroxyalkyl or halogenated lower alkyl; provided that R^7, R^8 and R^9 are not all hydrogen;

R^{10} is lower alkyl or halogenated lower alkyl;

and pharmaceutically acceptable salts thereof.

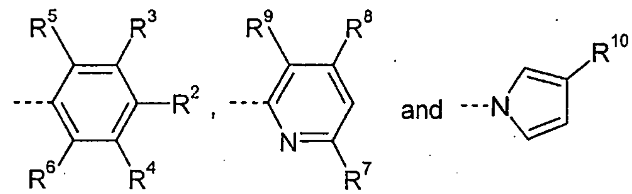
2. Compounds according to claim 1 having the formula (I)



(I)

wherein

R^1 is selected from



R^2 is hydrogen or lower alkoxy;

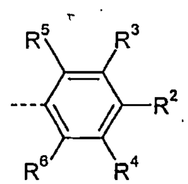
R^3, R^4, R^5 and R^6 are each independently selected from hydrogen, lower alkyl, halogenated lower alkyl, halogen or cycloalkyl; provided that R^2, R^3, R^4, R^5 and R^6 are not all hydrogen;

R^7, R^8 and R^9 are each independently hydrogen, lower alkyl or lower alkoxy;

R^{10} is lower alkyl or halogenated lower alkyl;

and pharmaceutically acceptable salts thereof.

3. Compounds according to claims 1 or 2, wherein R^1 is



and R^2, R^3, R^4, R^5 and R^6 are as defined in claims 1 or 2.

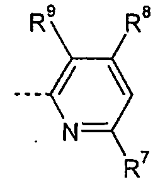
4. Compounds according to claim 3, wherein R^2, R^4, R^5 and R^6 are hydrogen and R^3 is lower alkyl, halogenated lower alkyl, halogen or cycloalkyl.

5. Compounds according to claim 4, wherein R^2, R^4, R^5 and R^6 are hydrogen and R^3 is lower alkyl, halogenated lower alkyl or halogen.

6. Compounds according to claim 3, wherein R^2, R^4 and R^5 are hydrogen and R^3 and R^6 are each independently lower alkyl, halogenated lower alkyl, halogen or cycloalkyl.

7. Compounds according to claim 3, wherein R^2, R^4 and R^5 are hydrogen and R^3 and R^6 are each independently lower alkyl or halogen.

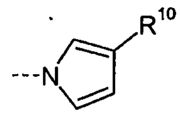
8. Compounds according to claims 1 or 2, wherein R^1 is



and R^7, R^8 and R^9 are as defined in claims 1 or 2.

9. Compounds according to claim 8, wherein R^7 and R^9 are hydrogen and R^8 is lower alkyl or lower alkoxy.

10. Compounds according to claims 1 or 2, wherein R^1 is



and R^{10} is as defined in claims 1 or 2.

11. Compounds according to any of claims 1 to 10, selected from the group consisting of:

rac-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ylamine hydrochloride,

rac-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

9,10-dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-m-tolyl-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

9,10-dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

9,10-dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-(6-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(6-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-9,10-dimethoxy-3β-(5-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(5-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-9,10-dimethoxy-3β-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

9,10-dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(R)-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyridin-2-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(4-ethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-ethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(3-cyclopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(6-methoxy-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-isopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(3-cyclopropyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-methoxy-2-methyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyrrol-1-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine hydrochloride,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride,

rac-[2-(2α-amino-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-3β-yl)-pyridin-4-yl]-methanol,

rac-3β-(4-fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride,

rac-3β-(4-fluoromethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

and pharmaceutically acceptable salts thereof.

12. Compounds according to any of claims 1 to 10, selected from the group consisting of:

9,10-dimethoxy-3(R)-m-tolyl-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-m-tolyl-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(S)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(S)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

9,10-dimethoxy-3(R)-(4-methyl-pyridin-2-yl)-1,3,4,6,7,11b(R)-hexahydro-2H-pyrido[2,1-a]isoquinolin-2(S)-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(4-ethyl-pyridin-2-yl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-3β-(2,5-dimethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine hydrochloride,

rac-3β-(3-chloro-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine hydrochloride,

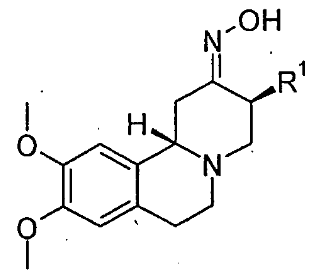
rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2β-ylamine,

rac-3β-(3-fluormethyl-phenyl)-9,10-dimethoxy-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

rac-9,10-dimethoxy-3β-(3-methyl-pyrrol-1-yl)-1,3,4,6,7,11bβ-hexahydro-2H-pyrido[2,1-a]isoquinolin-2α-ylamine,

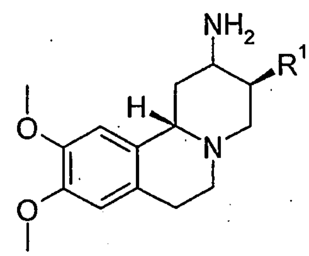
and pharmaceutically acceptable salts thereof.

13. A process for the manufacture of compounds of formula (I) as defined in any of claims 1 to 12, which process comprises converting a compound of the formula



wherein R^1 is as defined in claims 1 or 2;

into a compound of formula (I)



(I)

wherein R^1 is as defined in claims 1 or 2.

14. Compounds according to any of claims 1 to 12 when manufactured by a process according to claim 13.

15. Pharmaceutical compositions comprising a compound according to any of claims 1 to 12 and a pharmaceutically acceptable carrier and/or adjuvant.

16. Compounds according to any of claims 1 to 12 for use as therapeutic active substances.

17. Compounds according to any of claims 1 to 12 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with DPP-IV.

18. A method for the treatment and/or prophylaxis of diseases which are associated with DPP-IV such as diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, hypertension, diseases wherein a diuretic agent has a beneficial effect, obesity, and/or metabolic syndrome or β-cell protection, which method comprises administering a compound according to any of claims 1 to 12 to a human being or animal.

19. The use of compounds according to any of claims 1 to 12 for the treatment and/or prophylaxis of diseases which are associated with DPP-IV.

20. The use of compounds according to any of claims 1 to 12 for the treatment and/or prophylaxis of diabetes, non-insulin-dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, hypertension, diseases wherein a diuretic agent has a beneficial effect, obesity, and/or metabolic syndrome or β-cell protection.

21. The use of compounds according to any of claims 1 to 12 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with DPP-IV.

22. The use of compounds according to any of claims 1 to 12 for the preparation of medicaments for the treatment and/or prophylaxis of diabetes, non-insulin-dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, Colitis Ulcerosa, Morbus Crohn, hypertension, diseases wherein a diuretic agent has a beneficial effect, obesity, and/or metabolic syndrome or β-cell protection.

23. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006336

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/4745 A61P5/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/055881 A (HOFFMANN LA ROCHE) 10 July 2003 (2003-07-10) Abstract; claims; examples, e.g. nos. 44, 60-68, 80-85.	1-22
A	US 6 172 081 B1 (DAMON ROBERT) 9 January 2001 (2001-01-09) Abstract; claims.	1-22
A	US 4 550 114 A (WHITE JOHN F) 29 October 1985 (1985-10-29) Abstract; claims.	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2004	04/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/006336

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 18-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/006336

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03055881	A	10-07-2003	WO 03055881	A1	10-07-2003
			US 2003149071	A1	07-08-2003
			US 2004176406	A1	09-09-2004
US 6172081	B1	09-01-2001	NONE		
US 4550114	A	29-10-1985	GB 2134108	A ,B	08-08-1984

Form PCT/ISA/210 (patent family annex) (January 2004)